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(54) Formulations containing esculoside and the use thereof in the pharmaceutical and cosmetic fields

(57) The present invention relates to the use of esculoside alone or in combination with adenylate cyclase stimulators, such as forskolin or Salvia miltiorrhiza diterpenes and/or with phosphodiesterase inhibitors, such as apigenine-skeleton dimeric flavones, in topical formulations for the treatment of peripheral vasculopathies related to an impaired peripheral microcirculation, cellulitis or unesthetisms connected with a deposit of superfluous fat. For the reduction of the deposits of superfluous fat of any origin, the above mentioned products are advantageously also combined with caffeine, theophylline and derivatives thereof.

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Description

The present invention relates to formulations containing esculoside alone or in combination with adenylate cyclase stimulators, such as forskolin or Salvia miltiorrhiza diterpenes and/or phosphodiesterase inhibitors such as apigenin-skeleton dimeric flavones, for the topical use in the treatment of peripheral vasculopathies related to an impaired peripheral microcirculation; moreover, the invention relates to the use of esculoside alone or in combination with the cited adenylate cyclase stimulators and/or with the cited phosphodiesterase inhibitors in the treatment of cellulitis or unesthetisms connected with the deposit of superfluous fat. For the latter aspect, the above mentioned products can be added with caffeine, theophylline, pentoxifylline.

The invention also relates to the use of esculoside alone or in combination with adenylate cyclase stimulators, such as forskolin or Salvia miltiorrhiza diterpenes and/or phosphodiesterase inhibitors such as apigenin-skeleton dimeric flavones for the preparation of the above cited formulations.

Esculoside is a glucosidated coumarin extracted from the fruit pericarp and from the bark of Aesculus hippocastanum, and such a product has been used for a long time in the treatment of pathological conditions connected with an impaired permeability and capillary fragility and it is still used for the topical or systemic administration in the treatment of venous stasis vasculopathies, hemorrhoids and as a decongestionant in ophthalmology. Now it has surprisingly been found that esculoside, alone or in combination with the above cited products, when topically administered increases both arterial blood flow (activity on myocytes of arteries and precapillary arterioles increasing the sphygmicity thereof) in the administration area, and the number of perfused capillaries, thus improving the superficial and deep circulations. This phenomenon was measured by means of non-invasive techniques, such as infrared photopulsoplethysmography, laser Doppler flowmetry and computerized videocapillaroscopy. The first two techniques allow to evidence the vasomotility of the arteries and precapillary arterioles, whereas the latter permits to evaluate the changes in the capillary bed and the district angiotectonic. After recording the basal data, a placebo formulation or the formulation containing the active ingredient or the active principles are applied on the body area to treat, usually two symmetric body parts are used, randomizing the test. Immediately after the treatment, the treated areas are checked with a videocapillaroscope (Scopeman-Moritex Video Imaging System, Alfa Strumenti, Milan) fitted with a halogen-light optical probe with 50 to 400 x magnifications, measuring the capillary density (number of blood-perfused capillaries per surface unit) and evaluating the space orientation of the capillaries and the morphology thereof. The instrumentation was fitted with a videocamera for continuously recording the biomicroscopical images to allow the quantification of any changes during the elaboration phase. 20 Minutes after the treatment with esculoside alone or in combination with the products mentioned above, such as Ginkgo biloba dimeric flavones or amentoflavone, to cite the most important compounds, an increase in capillary density up to 200-300% took place, compared with the basal and placebo-treated control. The action of esculoside in concentrations ranging from 0.5 to 3%, evaluated as described above, lasts from one to three hours. Videocapillaroscopy, as mentioned above, allows to evaluate skin microangiotectonic, evidencing the number of perfused capillaries as well as the space orientation and stratification thereof.

It has surprisingly been found, and it is a part of the present invention, that, when formulations containing esculoside alone or in combination with compounds having adenylate cyclase stimulating activity or antiphosphodiesterase activity, and optionally also other lipolytic agents such as caffeine, theophylline, pentoxifylline, are administered to area affected with disorders due to chronic venous deficiency, such as cellulitis, or on deposits of superfluous fat such as the unesthetisms following a forced diet, a marked decrease in the pathology occurs thanks to the improvement of district microcirculation due to esculoside and to the lipolytic effect of the other components. The administrations are performed for times ranging from a few days to some months, usually three months, depending on the severity of the pathology or the unesthetism.

As far as the vascular system is concerned, esculoside alone or in combination with antiphosphodiesterase agents or adenylate cyclase stimulating agents can be used in chronic venous insufficiency, in Raynaud's disease and in acrocyanosis, as well as against cold-induced vasospasm, particularly at the level of fingers and toes microcirculation. The higher blood flow to the areas treated with said active principles affects favourably also skin early ageing, particularly face and neck skin, cellulitis-like derm-hypoderm panniculopathies and stretch marks (striae distensae); moreover the higher blood supply acts favourably also on not-glabrous skin, such as scalp, and is useful in the treatment of the primitive and secondary alopecias.

In the cosmetic fields, the main uses of the products object of invention relate the ageing of the skin and cellulitis, which affects a high percentage of population in the industrialized Countries.

By way of example of the above described uses, 20 patients suffering from chronic venous insufficiency (Stage I) were subdivided into two groups and treated with a formulation containing 1.5% esculoside or with placebo for 3 months, twice a day, administering the product from the throcanterian area to the ankle.

The patients, before the long-term treatment, were checked to evaluate their response capability by an acute test by means of videocapillaroscopic measurement of the increase in cutaneous microcirculation. The capillary density in the group treated with placebo, measured 20 minutes after the treatment, was $8.6 \pm 2.2\%$, whereas in the group treated with esculoside it was $18.6 \pm 3.1\%$, with $p<0.01$ calculated by Student test.

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The observed symptoms and their intensity, evaluated according to a severity score ranging from 0 to 4, are reported in the following tables:

Table I - Evaluation of the symptoms in patients affected with venous insufficiency of the leg, before and after a 3 months-treatment with 1.5% esculoside.

Patient No		1	2	3	4	5	6	7	8	9	10
Leg heaviness	Before:	0	0	3	2	2	1	3	1	2	0
	After:	3	2	4	1	4	2	4	2	4	2
Oedema	Before:	0	0	2	1	3	1	2	0	1	0
	After:	3	1	4	1	4	2	3	1	4	2
Paresthesia	Before:	1	0	2	0	0	0	1	0	3	1
	After:	2	0	0	0	0	0	2	1	1	0
Diurnal cramps	Before:	0	0	4	2	2	0	3	1	0	0
	After:	2	0	0	0	0	0	3	1	2	0
Nocturnal cramps	Before:	0	0	3	1	1	0	3	1	0	0
	After:	1	0	0	0	0	0	2	0	1	0
Venous telangiectasia	Before:	1	1	1	1	2	2	1	1	2	2
	After:	2	3	3	1	1	1	0	0	0	0
Varices	Before:	0	0	0	0	0	0	0	0	1	1
	After:	0	0	0	0	0	0	0	0	0	0
Nervous legs	Before:	0	0	4	1	3	0	4	2	3	1
	After:	4	2	2	0	3	0	1	0	1	0
Cold feet	Before:	3	2	4	1	4	2	4	1	4	2
	After:	4	2	4	2	4	2	3	1	4	2

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Table II

Means ± standard errors of the severity of the venous insufficiency symptoms before and after 3-months-treatment with 1.5% esculoside (statistic evaluation by means of Student t test for paired data).			
Symptoms	Before	After	P<
Leg heaviness	2.1 ± 0.38	0.9 ± 0.23	P< 0.01
Oedema	1.8 ± 0.33	0.6 ± 0.22	P< 0.01
Paresthesia	1.5 ± 0.34	0.3 ± 0.15	P< 0.01
Diurnal cramps	1.6 ± 0.48	0.4 ± 0.22	P< 0.01
Nocturnal cramps	1.1 ± 0.38	0.3 ± 0.15	P< 0.05
Venous Telangiectasia	1.5 ± 0.31	1.5 ± 0.31	N.S.
Varices	0.2 ± 0.13	0.2 ± 0.13	N.S.
Nervous legs	2.7 ± 0.42	0.7 ± 0.26	P< 0.01
Cold feet	3.7 ± 0.15	1.6 ± 0.16	P< 0.01

In thigh cellulitis due to chronic venous insufficiency, a 20 subjects group was treated from the throcanterian area to the ankle for three months with a formulation containing 1.5% esculoside, 0.3% of Salvia miltiorrhiza extract (this extract containing 15% tanshinone A2), 0.4% Ginkgo biloba dimeric flavones (prepared according to Indena Patent EP 0360556) and 0 2% theophylline. In these subjects, the observed parameters dramatically changed, as it is evidenced by the data reported in Figure 1.

In another test, a group of 20 subjects affected with fibrosclerotic panniculopathy of the trochanterian area with a deposit of superfluous fat was treated for 2 months with a formulation containing 1.5% esculoside, 0.3% Salvia miltiorrhiza extracts of and 1% pentoxifylline. The main control parameter was the reduction of the deposit of superfluous fat, therefore the diameter of the trochanterian area was measured; said diameter surprisingly decreased of 2.6 ± 0.2 cm.

A number of other tests were carried out changing the composition and the components ratios or the nature of the components, for the treatment of the above cited pathologies and unesthetisms. The formulations according to the invention contain, besides the above mentioned active principles, the conventional carriers, additives, preservatives and the like known in pharmaceutical technique, such as those reported in the following non-limiting examples.

Example I - Gel containing esculoside, Salvia miltiorrhiza extract and Ginkgo biloba dimeric flavones.

100 g of gel contain:

Salvia miltiorrhiza extract	0.30 g
Esculoside	1.50 g
Ginkgo biloba dimeric flavones	0.50 g
Hydrogenated castor oil 40(OE) (Cremophor RH40 - BASF)	1.00 g
Propylene glycol	1.50 g
Preservatives	0.10 g
Hydroxyethyl cellulose (Natrosol 250 HHX - Aqualon)	3.00 g
Purified water	q.s. to. 100 g

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Example II - Alcoholic fluid gel containing Salvia miltiorrhiza extract and caffeine.

100 g of gel contain :

Salvia miltiorrhiza extract	0.25 g
Esculoside	1.50 g
Caffeine	0.50 g
Hydrogenated castor oil 40(OE) (Cremophor RH40 - BASF)	5.00 g
Propylene glycol	3.00 g
Carbomer 940 (Carbopol 980 - Goodrich)	1.00 g
Ethanol	45.00 g
Phosphatidylcholine (Phospholipon 90-Natterman)	0.70 g
Gliceryl 6(OE)Caprilate/Caprinate (Softigen 767)	15.00 g
Preservatives	0.40 g
Butylhydroxytoluene	0.05 g
α-Tocopherol	0.20 g
Ascorbic acid	0.30 g
Dimethicone copolyol (SF 1188 - General Electric)	2.00 g
10% Triethanolamine sol.	5.00 g
Depurated water	q.s. to. 100 g

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Example III - Cream containing esculoside, Salvia miltiorrhiza extract and extract of Cola nut titrated in caffeine-like alkaloids.

100 g of cream contain:

Salvia miltiorrhiza extract	0.25 g
Esculoside	1.50 g
Cola nut dry extract (14% total alkaloids)	0.50 g
Hydrogenated castor oil 40(OE) (Cremophor RH40 - BASF)	2.00 g
Propylene glycol	2.00 g
Carbomer 934 (Carbopol 934 P - Goodrich)	0.50 g
Acrylates/Alkyl C_{10-30}-Acrylate crosspolymer (Carbopol 1382 - Goodrich)	0.50 g
Ethanol	15.0 g
Preservatives	0.40 g
Cetyl Palmitate (Cutina CP - Henkel)	8.00 g
Polyisoprene (Syntesqual - Vevy)	5.00 g
Polysorbate 80 (Tween 80 - ICI Americans)	2.00 g
α-Tocopherol	0.20 g
Ascorbyl palmitate	0.10 g
Hydrogenated lanolin (Lanocerina - Esperis)	5.00 g
Dimethicone 350 cps (Tegiloxan 350 - Tego)	0.50 g
10% NaOH sol.	2.40 g
Depurated water	q.s. to. 100 g

Example IV - Lotion containing esculoside and theophylline.

100 ml of lotion contain:

Esculoside	1.00 g
Theophylline	0.50 g
Butylhydroxytoluene	0.10 g
Ethyl alcohol 50°	q.s. to 100 ml

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Example V - gelified emulsion containing esculoside.

100 g of gelified emulsion contain:

Esculoside	1.00 g
Isopropyl myristate	5.00 g
Preservatives	0.40 g
Perfume	0.10 g
Polyacrylamide, C_{13-14} Isoparaffin and lauric alcohol 7(OE) (Sepigel 305 - Seppic)	3.00 g
Depurated water	q.s. to 100 g

Claims

1. Pharmaceutical and/or cosmetic formulations for the topical use, containing as the active principles esculoside combined with adenylate cyclase stimulators and/or phosphodiesterase inhibitors and/or lipolytic agents.

2. Pharmaceutical and/or cosmetic formulations according to claim 1, containing forskolin or Salvia miltiorriza diterpenes or mixtures thereof as adenylate cyclase stimulators.

3. Pharmaceutical and/or cosmetic formulations according to claims 1-2, containing apigenin-skeleton dimeric flavones as phosphodiesterase inhibitors.

4. Pharmaceutical and/or cosmetic formulations according to claim 3, wherein the flavones are selected from Ginkgo biloba dimeric flavones and amentoflavone.

5. Pharmaceutical and/or cosmetic formulations according to claims 1-4, containing caffeine, theophylline, pentoxifylline or mixtures thereof as the lipolytic agents.

6. Pharmaceutical and/or cosmetic formulations according to claims 1-5, for the treatment of peripheral vasculopathies related to an impaired peripheral microcirculation, of cellulitis and of unesthetisms connected with a deposit of superfluous fat.

7. The use of esculoside alone or in combination with adenylate cyclase stimulators and/or phosphodiesterase inhibitors and/or lipolytic agents for the manufacture of a medicament for the topical use, intended for the treatment of peripheral vasculopathies related to an impaired peripheral microcirculation, of cellulitis and of unesthetisms connected with a deposit of superfluous fat.

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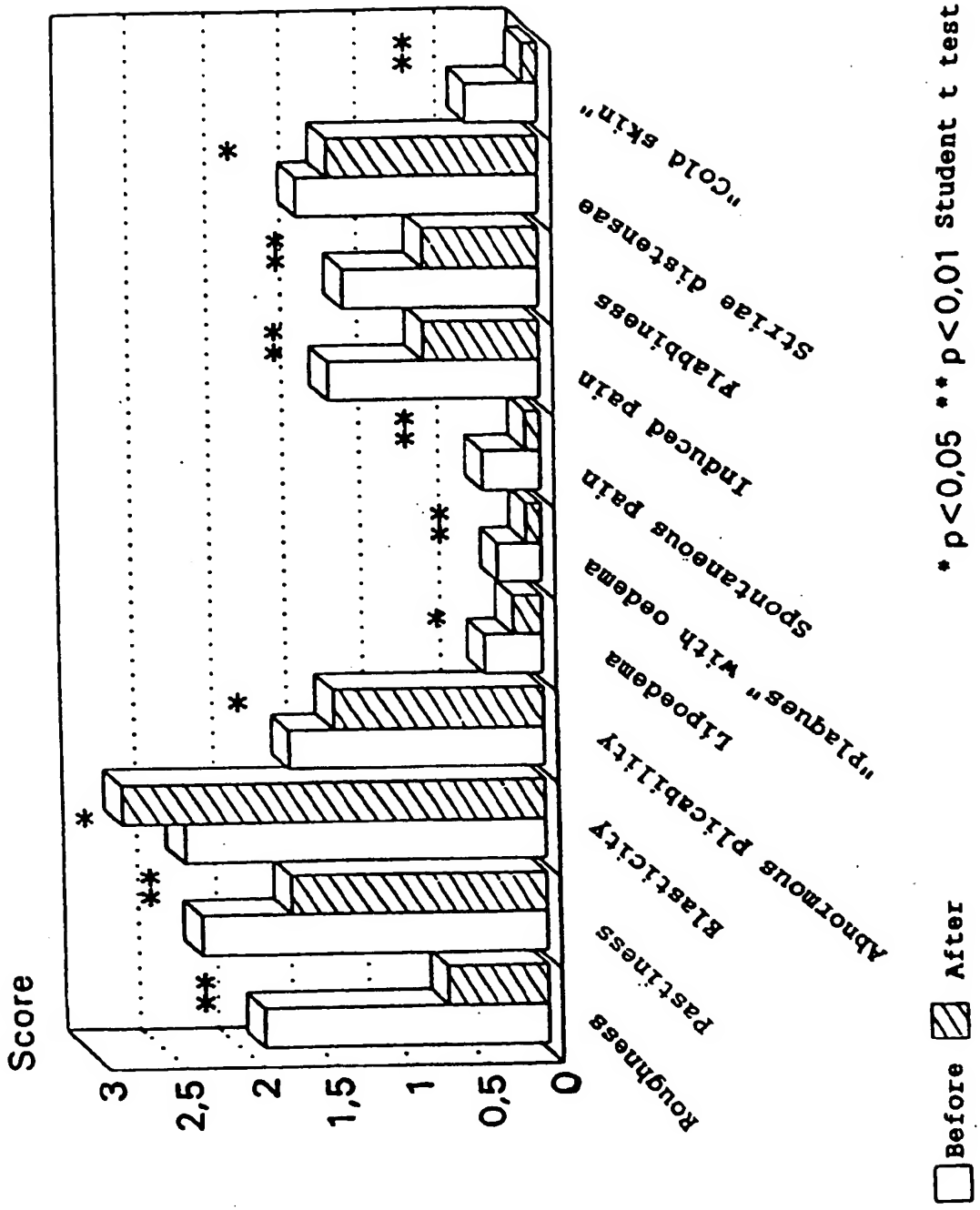
FIG. 1 - ANTICELLULITIS TREATMENT



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EUROPEAN SEARCH REPORT

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EP 95 11 0463

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	FR-A-2 583 640 (PASCAL BERDAL) * page 1; claims 1-3; example 1 * ---	1,4-7	A61K31/37 A61K35/78 A61K7/48
A	DE-A-19 39 008 (HELMUT ZANDER) * claim 2 * ---	1,5-7	
A	GB-A-2 092 445 (BIOTHERM) * abstract * -----	1,6,7	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	19 July 1996	Alvarez Alvarez, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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